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INTRODUCTION

Special issue on neutrophils

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For nearly a century, ever since their discovery by Metchnikoff, neutrophils have been viewed as mundane, plodding footmen of the immune system, not much unlike the archetypal London Bobby: first to arrive at the scene of a crime and to secure the situation by a cursory neutralisation of the intruding culprits. The true detective work, in this case the recognition and processing of foreign pathogenic antigens, would be assumed by the superintendent T and B lymphocytes.

This paradigm of the dull neutrophil and the immunologically exciting lymphocyte has seen challenges by a series of recent findings. Of these the most sensational was the discovery that neutrophils can extrude their genomic DNA into the extracellular environment as Neutrophil Extracellular Traps (NETs). While it was initially thought that NETs mainly served to ensnare and debilitate pathogenic microorganisms, they have truly opened up a new window to investigate neutrophil physiology.

As is evident from several reviews in this special issue on Neutrophils (Hahn et al., Mantovani et al., Branzk and Papayannopoulos), these specialized structures not only interact with bacteria or yeast, but also with multicellular eukaryotic parasites (*P. vivax* and *P. falciparum* in Malaria) and with viruses (HIV in AIDS).

Not unexpectedly, in a scenario reminiscent of a cold-war spy vs. spy thriller, both neutrophils and pathogens have developed an array of strategies and counter-strategies to secure or prevent entrapment and destruction. One of the most intriguing is the ability of HIV virions to induce the production of the immune modulating cytokine IL-10 by dendritic cells, which effectively hinders NETosis and normal neutrophil activity, thereby paving the way for frequently lethal secondary infections such as with *Mycobacterium tuberculosis*. On the other hand, in a process dubbed immune-thrombosis, the immune system may use components of the clotting cascade that interact with NETs to form tight complexes around invading pathogens.

It has also become evident that the host micro-environment plays a significant role in modulating neutrophil activity, including the respiratory system or systemic influences present in pregnancy (refer to Hahn et al.). The extent of neutrophil interaction is also be associated with the seeding of cancer stem cells, the process of metastasis and cancer progression (refer to Mantovani et al., and Geffner et al.).

In addition, a number of recent findings implicating aberrant neutrophil activity in a diverse array of human pathologies have rung the death knell of the arcane perception of the mundane, crude granulocyte. These include observations that neutrophil NETs may be implicated in autoimmune or auto-inflammatory conditions such as systemic lupus erythromatosus (SLE), anti-neutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis and gout, or contribute to the pathology of cystic fibrosis (refer to reviews by Carmon-Rivera and Kaplan, Marion and Radic, Ritis et al.). Indeed, it appears that neutrophils may exist in discrete forms or distinct sub-populations, such as low-density granulocytes, and that the latter may play a crucial role in the pathology of SLE (refer to Carmon-Rivera and Kaplan). The potential involvement of cytokines such as Activin-A in promoting neutrophil mediated inflammation is discussed by Sideras and colleagues.

These findings concerning overt or aberrant activity have fuelled the search for pharmacological agents to effectively tailor or modulate neutrophil behaviour; strategies targeting the cAMP or calcium signalling pathways or the inhibition of granular components are discussed in the reports by Anderson et al., and Kormacs et al., while the underlying signal transducing pathways involved in NETosis are

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discussed by Branzk and Papayannopoulos, as well as Geffner et al. Of particular interest is the discussion of several distinct forms of NETosis, including a rapid one that leaves the host cells intact as enucleated, but phagocytically functional spheroblasts. This discourse also provides an excellent insight into the roles of granular enzymes, neutrophil elastase and myeloperoxidase, in the NETotic process, such as clipping of the histones to mediate unravelling of the nuclear genomic DNA and disruption of the nuclear membrane prior to DNA extrusion.

While it is clear that there are many unexpected facets of neutrophil biology to be determined or explored, such as the recent observation that NETs associated peptidylarginine deiminases may provide a scaffold for citrullinated autoantigen production in rheumatoid arthritis (Carmon-Rivera and Kaplan), it is hoped that this special volume provides a useful kaleidoscopic snap-shot of current knowledge and research directions.

We thank the authors for their valuable contributions and trust the readers will enjoy this timely update.